Sex and cervical cancer

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Carcinoma of the cervix is a major health problem throughout the world. After breast cancer, it is the second commonest malignancy in women, with an incidence of about half a million cases a year. In some localities—Africa, India, and certain other Asian countries—it is the commonest cancer in women; in Europe and North America it is the fourth commonest.[1] Data from some developed countries show a reduction in cervical cancer mortality of about 30% between 1960 and 1980, presumably because of early diagnosis through screening programmes.[2] In England and Wales, however, there has been only a small decline in deaths from this cause in the past 20 years, and 2000 women a year still die of it.[3] During the past decade there has been a pronounced increase in cervical intraepithelial neoplasia (CIN), particularly in young women,[4][5] and Beral, using a computer model, has predicted a 60% increase in cervical cancer registrations and a 70% increase in mortality in women aged under 50 in 10 years' time.[6]

Squamous carcinoma of the cervix is the culmination of CIN, which is a series of progressive epithelial changes. Although the pathogenesis of these changes is not well understood, the cytology and histology of CIN is clear,[7] and invasive cancer of the cervix could be completely prevented if CIN was detected by screening tests and treated correctly. Epidemiological studies have made it possible to define some behavioural and other characteristics of women who are at relatively high risk of cervical cancer, and recent advances in basic science have clarified, at least in part, the aetiology of the disease. The purpose of this paper is to review this evidence with particular reference to women who attend clinics for sexually transmitted diseases, and to look for ways in which the services in these clinics can be used or modified to reduce the likelihood of invasive cervical disease in this group.

Epidemiological review

Domenico Rigoni-Stern was chief physician of a hospital in Verona, and he analysed mortality from cancer in that city for the years 1760–1839.[8] He pointed out that cancer of the uterus (and he was probably referring to the cervix) was commoner in married women and widows than in unmarried women, and was unknown in those bound by monastic vows. He suggested that the liability of a uterus to cancer might depend on "the natural exercise of its functions." It is difficult to be sure what he meant by this, but he was probably referring to either menstruation or childbirth. These observations were largely forgotten until quite recently, but in the early 1950s several studies confirmed the extreme rarity of carcinoma of the cervix in Catholic nuns.[9][10] In the discussion of these findings, emphasis was placed not on the celibacy of these women but on their childlessness, because at the time chronic cervicitis and cervical lacerations during delivery were regarded as being of major aetiological importance.

During the 1960s, links were noted between carcinoma of the cervix and prostitution. Studies of the inmates of women's prisons showed that the disease was four to six times commoner in these women than in the general population.[11][12] In London, Keighley found that 9% of a group of prostitutes in prison had cytological evidence of carcinoma in situ.[13] It was becoming clearer that there were links between carcinoma of the cervix and coitus. A series of case control epidemiological studies followed, in which associations were sought between the disease and factors relating to female sexuality.[11] The two key variables that discriminated between women with and without cervical cancer were found to be coitarche at the age of 17 or younger and the lifetime number of sexual partners. There were no associations with the frequency of coitus, patterns of menstruation, or with numbers of abortions, pregnancies, or deliveries. Associations between cervical cancer and marital instability, multiple marriages, and a history of sexually transmitted disease (STD) existed, but these were regarded as covariables of the number of sexual partners. The data support the idea that cervical

cancer is caused, in whole or in part, by one or more sexually transmitted agents. The relative importance of age at coitarche has been much discussed. It is argued that the cervical epithelium of a young woman, which is undergoing squamous metaplasia, is peculiarly vulnerable to the effects of sexually transmitted agents. If this were so, it would be expected that if coitarche was occurring at a younger age the incidence of cervical cancer would be likely to rise. Beral has observed that, although there are no data on changes in age at coitarche in successive generations of women, the average age at first marriage, which is a related variable, fell from 25·8 years in 1921 to 22·4 years in 1971, but a corresponding increase in mortality has not been found.[14] It is obviously important to try to disentangle the correlated factors of age at coitarche and number of sexual partners. When this was done in a case control study of CIN, the number of partners emerged as an independent risk factor.[15]

A doctor working in the late 1980s must be impressed by the readiness with which his predecessors attributed cervical cancer to female promiscuity, rather as Victorian doctors attributed venereal disease to prostitution. In both cases, of course, male sexual behaviour is an important risk factor; in many societies, the risk of a woman developing cervical cancer depends as much, or more, on her partner's sexual behaviour as on her own.

Male factors

CIRCUMCISION
As early as the eighteenth century, Jewish women were recognised as having a low risk of cervical cancer, despite multiple pregnancies and often poor living conditions.[16] Subsequent studies confirmed the low incidence of the disease in Jewish women living both in Israel and elsewhere,[17 18] and this was variously attributed to genetic factors, diet, or adherence to Mosaic law. In the Fiji islands in the 1930s a lower incidence of cervical cancer was noted in native Fijians, whose partners were circumcised, than in resident Indian women, whose partners were not. Handley suggested that the preputial sac might harbour potentially oncogenic bacteria or other agents,[19] which might explain the relative freedom of Jewesses from cervical malignancy. In the 1950s several attempts were made to induce neoplasms in animals by the inoculation of human smegma, with unconvincing and contradictory results. In his analysis of a series of epidemiological studies conducted to test the circumcision hypothesis, Rotkin concluded that "there is little likelihood that non-circumcision of sexual partners increases the risk of cervical cancer to any extent."[20]

The relatively low risk of carcinoma of the cervix in Jewish women is therefore unexplained, although it has been observed that those who do develop the disease tend to have the same risk factors as other women.[18 21] Perhaps the explanation lies in endogamous marriages and monogamous patterns of sexual behaviour, as suggested by Martin.[22]

MALE SEXUAL BEHAVIOUR
The importance of the "male factor" in the aetiology of cervical cancer has been emphasised in several studies. Beral noted high mortality in the wives of men whose work entailed travel and prolonged absences from home,[14] who might be more likely to engage in extramarital intercourse. Buckley *et al* studied a group of women who had had intercourse with only their husbands, and found that the risk of cervical neoplasia increased with the number of other sexual partners of the husbands.[23] Skegg *et al* noted the extremely high incidence of cervical cancer in some parts of Latin America, in contrast with the substantial decline in mortality in many western industrialised societies during the past half century.[24] They suggested that in societies where marital fidelity is expected in women, whereas premarital and extramarital intercourse is common and tacitly approved in men, the sexual transmission of oncogenic agents might lead to high levels of cervical cancer. This could be the case in parts of Latin America. In Europe, on the other hand, a change in male sexual behaviour, particularly in relation to prostitution, may have led to the general decline in cervical cancer mortality. This decline was, however, interrupted in women born between 1911 and 1926, who were young adults during the second world war when the incidence of STD was high,[14] and again with the later advent of the "permissive society." Kessler sought an answer to the question: Is the risk of developing cervical cancer greater in the wives of men who at some time in their lives were married to other women with cervical cancer?[16] Preliminary data indicated the existence of such associations; "marital clusters" were identified in which two wives of one man developed cervical neoplasms more often than could have happened by chance.

SOCIAL CLASS AND OCCUPATION
In the United Kingdom, a married woman's social class is determined by her husband's occupation. Beral analysed standardised mortality from cervical cancer and found that there was a clear social class gradient, death from the disease being much commoner in the wives of unskilled labourers than in the wives of professional men.[14] Furthermore, there was a wide range of standardised mortality within each social class, the highest rates being found in the wives of husbands whose work entails travel away from home, such as long distance lorry drivers and fishermen, in

whom STDs, which are indicative of extramarital intercourse, are relatively common.

CERVICAL CANCER AS AN STD

There is some evidence of an association between carcinoma of the penis and of the cervix in marital partners. Several workers in Puerto Rico, New York State, and London have reported a significant excess of deaths from cervical cancer in the wives of men with penile cancer,[25-27] and some cases of cancer in these two sites may have a common aetiology. Interestingly, whereas circumcision gives protection against penile cancer, it is not established as protecting women from cervical cancer. The sexual transmission of an oncogenic agent might be prevented by barrier contraception, and Rotkin cites five studies that indicate that condoms and diaphragms are used less often, and withdrawal or no attempt at contraception more often, by patients with cervical cancer than by controls.[20] Beral has observed that mortality from cervical cancer rose and fell at rates consistent with the rise and fall in the incidence of the classical venereal diseases, gonorrhoea and syphilis 20 years previously. This also suggests that the sexual transmission of an aetiological agent plays a part in the pathogenesis of cervical cancer.

Aetiology

One agent alone is most unlikely to cause cervical cancer. In general, malignancy is now believed to result from the interaction of a whole series of host and exogenous factors operating over time. Thirty or 40 years ago research was more concerned with the pursuit of individual variables, and several sexually transmitted micro-organisms were studied in the search for a "cause" of cervical cancer. For example, it was noted in the 1940s that women with cervical cancer were more likely to have syphilis than the general population,[28] but promiscuity was a confounding variable and when this was taken into account the association disappeared.[29] Similarly, a role for *Trichomonas vaginalis* was suspected at one time, as trichomoniasis may be associated with cervical atypia or even with invasive carcinoma.[30] It is now accepted that the infection and cervical neoplasia are more likely to be covariables of promiscuity.

CHLAMYDIA TRACHOMATIS

C trachomatis is an obligate intracellular parasite that is a common cause of inflammatory cervical disease.[31] Ultrastructure studies have shown the presence of the organism at the squamocolumnar junction.[32] Chlamydial infections are inherently chronic and, once established in the cervix, can persist for many months.[33] Could they have an oncogenic potential?

Several seroepidemiological studies have shown associations between *C trachomatis* and cervical dysplasia, women with dysplasia showing higher titres than controls.[34 35] In studies of this kind matching controls for sexual factors, particularly the number of partners, is essential. Schachter *et al* reported that the excess of chlamydial antibodies in women with dysplasia still held good when they were carefully matched with controls for numbers of sexual partners. There is no evidence of an association between cervical dysplasia and the synchronous isolation of *C trachomatis*.[36]

Briggs and Paavonen have pointed out that the interpretation of the cytology results reported in association with chlamydial infection is clouded by the varying criteria used to define "cervical atypia."[37] The meaning of the abnormalities is uncertain. Some may be an early part of the CIN continuum, but others may represent an epithelial reparative process after damage by infection. Only careful prospective studies will resolve this dilemma. Until then, judgment on the possibility of an oncogenic role for *C trachomatis* must be reserved.

VIRAL INFECTION

If a sexually transmitted infectious agent plays a part in the pathogenesis of cervical cancer, it is more likely to be a virus than a protozoon or bacterium. Several types of virus are known to cause cancer in animals,[38] and viral infection appears to be a necessary part of the multifactorial aetiology of some malignancies in man. Although exposure to the virus is a primary risk factor, the number of people so exposed far exceeds the number developing malignancy, so that cofactors must determine the outcome. This is exemplified by infection with Epstein-Barr virus (EBV), which is widespread throughout the world. In tropical Africa, however, a secondary environmental factor, holoendemic malaria, influences the development of Burkitt's lymphoma, and in China a secondary host factor, HLA haplotype, influences the development of nasopharyngeal carcinoma.[39] It is difficult to prove that a virus has an oncogenic role in man, because some viruses might simply persist as non-oncogenic passengers. The persistent expression of viral DNA sequences in tumour cells certainly suggests a causal link, particularly if the viral DNA sequences are integrated into the genetic material of the host cell. The presence of viral antibodies in patients with malignant disease would be important only if the antibody titre was higher than in control subjects, and if the development of antibodies could be shown to precede the appearance of the cancer.

During the past 20 years, much effort has been directed to studying two viruses that may be oncogenic to the cervix, first herpes simplex virus type 2 (HSV2),

then more recently specific types of human papillomavirus (HPV).

Herpes simplex virus

Herpes viruses can be oncogenic both in animals and man.[40] The suggestion that HSV2 might play a part in the pathogenesis of cervical cancer was initially based on seroepidemiological studies that showed that the prevalence, and in some studies the titre, of antibodies was greater in women with invasive and preinvasive disease than in control groups. Of about 30 such case control studies performed throughout the world, only six have failed to show this difference.[41] There is, however, some difficulty in finding strength and consistency in these investigations. Even in positive studies, up to half the women with invasive cervical cancer may not show detectable antibodies.[41] The problems with studies of this kind are: firstly, the comparability of the different methods used to detect viral antibodies; secondly, the difficulty, with some serological techniques, of distinguishing between HSV2 and HSV1 antibodies; and thirdly, the failure, in many of the studies, to match the test and control groups for sexual experience. In the few studies that did this, however, correlation between HSV2 antibodies and cervical neoplasia was still found.[42]

Molecular biological data concerning HSV2 and cervical cancer, which fit a classic model of a tumour induced by DNA virus, have proved difficult to collect. In the laboratory, DNA sequences of HSV2 are capable of transforming rodent fibroblasts in culture into cells resembling tumour cells.[43] In human material, although antigens specific to HSV and RNA specific to HSV2 have been detected in CIN and cervical cancer cells,[44 45] detecting episomal or integrated HSV DNA sequences has been very difficult.[39] To reconcile these conflicting data, Galloway and McDougall support the theory that HSV initiates, but does not maintain, transformation—the so-called "hit and run" hypothesis.[46]

Some prospective clinical studies have been performed. Detailed investigation of a group of women attending an STD clinic in Oxford failed to show an excess of dyskaryotic changes in those with current HSV infection compared with other groups.[47] Some of the women were examined again up to four years later, but again no excess of CIN was found in those with herpes. Vonka *et al* prospectively studied a large group of patients and found no evidence that the presence of HSV2 antibodies, either on entry or up to four years later, was associated with the development of cervical neoplasia.[48] On the other hand, Nahmias *et al* reported that a group of women with HSV2 antibodies followed up prospectively showed a greater risk of cervical neoplasia than women without antibodies.[49]

At one time HSV2 was thought to fit the requirements of a sexually transmitted carcinogen quite well, but now there are doubts. There is only limited evidence that the results of the seroepidemiological studies cannot be explained by differences in sexual behaviour, and some authorities find the virological data convincing. HSV2 is no longer thought to be a possible sole cause of cervical cancer. It may act as an initiator or promoter in conjunction with HPV, bit it may be simpler to apply Occam's razor and conclude that HSV does not play any appreciable part in cervical cancer.[39]

Human papillomavirus

In contrast with HSV, the evidence suggesting a causal role for HPV in cervical neoplasia comes predominantly from molecular virology. Papillomaviruses are oncogenic in some animals.[50] In man they are a heterogeneous group, and DNA hybridisation studies have shown that there are more than 40 types.[51] HPV 6 and 11 are associated with clinical and subclinical genital warts and with mild cervical dysplasia (CIN 1 and 2). HPV 16 and 18 are consistently associated with invasive cervical, vulval, or penile cancers and the higher grades of dysplasia.[52 53] HPV 31 has been found in some patients with CIN, mostly in North America.[54] HPV 16 or 18 have also been found in some cell lines originally derived from cervical cancers.[52] In these cell lines, and in invasive cancer, the viral DNA sequences are integrated into the host cells, whereas in benign and premalignant lesions the DNA is episomal.[55] HPV structural proteins have been found in a large proportion of CIN biopsy specimens.[56] In general the histology of genital lesions correlates well with the presence of specific viral types, but about 10% of benign condylomas contain sequences of HPV 16 or 18, and some carcinomas contain sequences of HPV 11.[51] Furthermore, mixtures of viral types have been reported in some biopsy specimens,[57 58] and 10–30% of women with colposcopically and histologically normal cervices show sequences of HPV 16.[59–61]

Seroepidemiological evidence to support the role of HPV in the pathogenesis of cervical cancer is very limited, as classic serological testing has been impossible because HPV cannot be propagated in the laboratory to provide a source of antigen. A group reactive antigen obtained from bovine papillomavirus type 2 has, however, been used in an enzyme immune assay system.[62] Antibodies were detected in 95% of patients with anogenital warts, 60% of those with CIN, 93% of those with cervical cancer, and 0–7% of various control groups.

Further evidence supports a role for HPV genotypes in the pathogenesis of cervical neoplasia. Malignant transformation of benign genital warts has been described many times.[63] CIN is associated with vulval warts[64] and with cervical HPV infection.[65] A prospec-

tive study has shown that women with cytological evidence of HPV as the sole cervical abnormality are 15 times more likely to progress to CIN than are controls.[66] Progression of minor degrees of dyskaryosis to CIN 3 are more likely if associated with HPV 16 than if associated with HPV 6.[58] An increased risk of CIN in the consorts of men with penile condylomas has been reported.[67] Transformation of NIH3T3 cells in vitro by DNA sequences of HPV 16 has been described.[68] Genital warts are known to be sexually transmissible,[69] and although individual HPV types have not been proved to be sexually transmitted, it seems to be a reasonable assumption. All this evidence has convinced many workers that certain HPV types may be the sexually transmitted carcinogens that have been sought for so many years.

Nevertheless, the data are in some respects incomplete, and not totally convincing. The numbers of patients with cervical cancer and controls in whom the various HPV types have been identified are mostly small, and some of the differences could have arisen by chance. The controls are often not satisfactorily matched for age, socioeconomic status, sexual activity, or other relevant variables. One study showed no difference in HPV 16 sequences, after age adjustment, between patients with cervical cancer and controls.[70] Data on the association of HPV with CIN also come from small numbers of patients about whom there is often little or no demographic information. A further problem in interpreting the data is that comparison between various groups may be partly invalidated by different methods of collecting cervical material (such as biopsy or cervical scrape) and by the use of hybridisation methods (such as Southern blot or dot blot), which may differ in sensitivity and specificity.

Regarding the prospective studies, Franceschi *et al*[47] have pointed out that, although CIN 3 is more sinister than superficial dyskaryosis, it is still not a malignant neoplasm; the causes of progression of CIN 3 to invasive cancer are not known, and are not necessarily the same at the causes of progression from a normal cervix to CIN 3. The current high prevalence of CIN 3 (and indeed of vulval, penile, and anal intraepithelial neoplasia) possibly simply reflects an epidemic of infection by HPVs that produce lesions that mimic "genuine" CIN, but are inherently harmless.[71] The high prevalence of HPV sequences in women with normal cervices may be thought to cast doubt on their oncogenic role.[72] This argument may not be valid because, in general, the number of people infected with oncogenic viruses, such as EBV and hepatitis B viruses, far exceed the number who subsequently develop cancer. The prevalence of HPV in normal cervices is a problem only if a sole cause of cervical cancer is sought. Current opinion, based on

knowledge of viral oncogenesis, is that if specific HPV types are causally associated with cervical cancer there is one or more cofactor.

HPV 16 was identified five years ago, and HPV 18 four years ago, which has not given enough time to define their role in cervical neoplasia. Further research, including well controlled prospective studies, with standardised and reproducible laboratory procedures, will be needed to clarify these problems. Enough information is, however, already available to make these efforts well worth while.

NON-INFECTIVE FACTORS

Cigarette smoking
Cigarette smoking is quite strongly associated with the risk of both invasive cervical cancer and CIN.[16 73] The possibility that this association is the result of confounding it with sexual behaviour has been considered, but smoking persists as a risk factor after adjustment for age at coitarche and numbers and sexual background of sexual partners.[16 23 74] Both nicotine and its major metabolic, cotinine, can be detected in the cervical fluid of cigarette smokers.[75]

Sperm proteins
Ten years ago Reid suggested that basic proteins from human spermatozoa might induce neoplastic transformation of cervical epithelial cells,[76] and the addition of human sperm protamine to cervical cell cultures may induce transformation in vitro.[77] A lower risk of cervical cancer in women whose partners have had vasectomies has been recorded.[78] The amount of sperm basic proteins differs in individual men,[79] and carriage of high concentrations of these proteins may be one aspect of "high risk" men.[80]

Oral contraceptives
An association between oral contraception and cervical neoplasia has not been established.[16] Epidemiological studies are difficult because of the large number of confounding variables, such as age, coital factors, reasons for adopting oral contraception, and the problems of establishing appropriate control groups. If there is an association, it is likely to be weak.

Immunological factors
An association between iatrogenic immunosuppression and CIN has been described several times in renal transplant recipients. Schneider *et al* found a 4·5% prevalence of CIN in this group, which was seven times more than in non-immunosuppressed patients.[81] Depression of immune function has been described in homosexual men without HIV infection who practise frequent anal intercourse,[82] and Frazer *et al* postulated

that this might be due to the burden of other infections.[83] Whether antigen overload similarly causes impaired immunity in women, and whether this might be a factor in cervical carcinogenesis, is not known.

Discussion

How can the knowledge of the epidemiology and aetiology of cervical cancer that has accumulated in recent years be applied in clinical practice? This question can be answered by considering general prophylaxis by screening for preinvasive disease, specific prophylaxis by intervention against known or suspected aetiological agents, and health education.

SCREENING PROGRAMMES

Cytological screening for cervical neoplasia has been in use for over 30 years, and remains the mainstay of control. During the past decade this has been supplemented by colposcopy for women found to have abnormal smears.[84] Good control programmes have a major effect in reducing deaths from cervical cancer. This has been shown many times, for example in studies of time trends in mortality from the disease in Nordice countries.[85] In 1965–82 in Sweden, where there is a nationwide programme, mortality fell by 50%; in Denmark, where 40% of the population are covered by organised programmes, there was a fall of 25%; but in Norway, with only 5% of the population covered, the mortality fell by merely 10%. In the United Kingdom there is no generally applied screening programme, and in 1974–82 deaths from cervical cancer decreased by 7%.[86 87]

Like other biological procedures, cervical cytology can be inaccurate. The proportion of false negative reports may be as high as 30%,[88] because of either inadequate sampling of the cervix or human error. In principle, this underdiagnosis can be compensated by regularly repeated screening, but this is unsatisfactory. The automation of cytology or the development of new techniques, such as cervicography or biochemical tests for dysplasia, however, may substantially reduce false negative reporting. A further problem lies in the lack of correspondence between cervical cytology and histology results. Women may have more severe abnormalities than had been expected from initial screening, and mildly atypical cervical appearances may be associated with CIN3 or even invasive cancer.[89 90] The use of colposcopy to investigate women with any type of abnormal smear would resolve this difficulty, although there are obviously major difficulties of logistics.

Screening is most effective when concentrated on women who are at high risk of cervical neoplasia. Women who attend clinics for STD are not a homogeneous group, but most are young, they or their partners, or both, have multiple sexual contacts, and they do not use barrier contraception. This subgroup shows the epidemiological characteristics of a "high risk" group, and it is surprising that they have been so little studied. The available data are difficult to interpret because varied criteria are used to select patients for screening, the methods used differ, and there are few satisfactory population based controls. Maw and Hanley, who had a consistent policy of performing cytology on women attending an STD clinic in Belfast if they had not undergone cytology elsewhere for a year, reported that the proportion of dysplastic smears was not only consistently higher than in family planning clinics in the area but had also shown a steady increase during the years 1970–81.[91] Briggs *et al* found that the prevalence of abnormal cytology results in an STD clinic in Seattle was over five times that reported in a national screening programme.[92] Lyttle *et al* discovered abnormal smears in 14·6% of an unselected group of women attending an STD clinic in Christchurch, New Zealand.[93] These data show that cytological screening in STD clinics is essential. The proportion of clinics in the UK that offer this service is not known. A self selected group of 116 clinics replied to a questionnaire as follows: 54 performed routine cytology for all new patients; 23 did so only for patients who had not undergone cytology elsewhere during the preceding year; 35 undertook selective screening based on age, indications of a cervical abnormality, or other factors; and four did not perform cytology at all.[94] These figures probably overstate the provision of cytology in STD clinics nationwide, as those already undertaking cytology would be more likely to want to take part in a study of this kind.

If colposcopy of all women with abnormal smears is now thought to be advisable, generating large numbers of these smears from STD clinics will cause major problems. In most parts of the world colposcopy units, if available, are already heavily committed. One possible solution is to arrange for colposcopy in STD clinics. This is already undertaken in some units. It is obviously important that colposcopists are fully trained, and that facilities are available for cervical biopsy specimens to be taken. It is also essential that there is a clear working agreement with local gynaecologists about the treatment of preinavasive cervical disease. Histologically confirmed CIN 1 or 2 could be treated in the clinic by cryotherapy or other means. The treatment of CIN 3, the management of patients with abnormal smears whose cervices cannot be satisfactorily seen at colposcopy, and the treatment of patients with extensive multifocal disease all require the intervention of a gynaecologist, and before colposcopy is started in an STD clinic such collaboration must be ensured.

In the UK there has recently been public concern about the efficacy of current procedures for cercival cytopathology screening, and proposals have been made for the implementation of a national computerised programme of call and recall for screening by cervical cytology and the introduction of a standard computerised system for histopathology records.[95] Admittedly, there are disadvantages in traditional cervical cytology, but this has been the basis of cervical cancer prevention for many years, and has achieved great success in some countries. Until the practicality and efficacy of alternative screening techniques such as cervicography have been established it is better to press for improvements in existing procedures rather than advocate new ones.

There can be no doubt that cervical cytology, supplemented by colposcopy, should be available for women who attend STD clinics, and in these high risk groups yearly screening is usual[94] It is important that all women should be informed of the results of their tests, and that those with reported abnormalities are recalled for further investigations. In most clinics a system already exists for the recall of patients who require further treatment or surveillance. Reporting the results of cervical cytology to patients' general practitioners, and enrolling women attending STD clinics into a national computerised cervical cytology service, when such exists, raise important ethical issues concerning confidentiality, which have not yet been addressed. For effective cervical cancer control these women, many of whom are at high risk, should clearly be included in a call and recall system and their general practitioners should know the results of their cytology. The problem of how to achieve this without breach of confidence regarding attendance at an STD clinic requires urgent consideration.

SPECIFIC PROPHYLAXIS

Preventing cervical neoplasia by identifying and treating causal agents, or by immunisation against such agents, is an attractive hypothetical idea. If specific HPV genotypes are accepted as necessary agents in the pathogenesis of the disease (admitting the existence of one or more cofactors), would their identification assists clinicians? DNA hybridisation has been proposed as an adjunct to cervical cytology; the detection of HPV 16 has been said to identify women at high risk of rapid progression of mild cervical atypia, and these women should be treated promptly regardless of age.[58] If these ideas are correct, the sensitivity and specificity of hybridisation tests, for which kits may soon be commercially available, will be of crucial importance; errors might result in a woman being subjected to unnecessary surgery. In 1983 Kaufman *et al* concluded that until more information is available on the natural history of lesions associated with HPV, dysplasia associated with clinical or cytological evidence of HPV infection should be treated no differently from dysplasia without such evidence[96] It may well be prudent to extend these observations to include DNA indentification, and to await further clarification before hybridisation is used as a complement to cervical cytology.

Women who have genital warts or partners with genital warts often show evidence of CIN.[64 67] For this reason, identifying, by standard contact tracing methods, the sexual partners of men attending STD clinics with penile warts, followed by their clinical examination and cervical cytology, is most desirable. Whether the comprehensive treatment of penile and vulval warts would ultimately reduce the incidence of CIN is an open question, but these lesions are mostly due to infection by the "low risk" genotypes HPV 6 and 11. Obsessive treatment of all genital warts, even if it was effective, might make little difference to levels of CIN. As there is no convincing that other genital infections are aetiologically connected with CIN, their presence does not indicate the need for any investigation for CIN or for surveillance, other than routine cytology.

HEALTH EDUCATION

Until the advent of the acquired immune deficiency syndrome (AIDS), health education about sexually transmitted diseases received little attention or resources. Now many countries have developed public education programmes regarding AIDS, emphasising the risks of sexual promiscuity and advocating the more general use of condoms. In the long run, these programmes may help to reduce the incidence of cervical neoplasia. Many countries also have health education programmes relating to cervical neoplasia, emphasising the need for all women to undergo regular cytology, and explaining what is involved. Some coordination of these programmes should be considered. STD clinics offer good opportunities for health advice, both generally to prevent STD and specifically to prevent cervical cancer. It seems virtually certain that the incidence of CIN will continue to escalate in the forseeable future, and workers in STD clinics will have an important role in its early diagnosis and prevention.

References

1 Control of cancer of the cervix uteri—a WHO meeting. *Bull WHO* 1986;**64**:607–18.
2 Cancer in developed countries: assessing the trends. *WHO Chronicle* 1985;**39**:109–10.
3 Elwood JM, Cotton RE, Johnson J, Jones GM, Curnow J, Beaver MW. Are patients with abnormal smears adequately managed? *Br Med J* 1984;**289**:891–3.
4 Ward BG, Shepherd JH, Monaghan JM. Occult advanced cervical cancer. *Br Med J* 1984;**290**:1301–2.

5 Roberts A. Cervical cytology in England and Wales, 1965–1980. *Health Trends* 1982;**14**:41–3.

6 Beral V, Booth M. Predictions of cervical cancer incidence and mortality in England and Wales. *Lancet* 1986;i:495.

7 Anderson MC. The pathology of cervical cancer. In: Singer A, ed. *Cancer of the cervix: diagnosis and treatment. Clin Obstet Gynecol* 1985;**12**:87–119.

8 Rigoni-Stern D. Fatti statistici relativi alle malattie cancerose che servivono di base alle poche cose dette dal dottore. *Giornale Servire Progresso Patologia i Terapia* (Series 2) 1842;**2**:507–17.

9 Gagnon F. Contribution to the study of etiology and prevention of cancer of the cervix of the uterus. *Am J Obstet Gynecol* 1950;**60**:516–22.

10 Fraumeni JF, Lloyd JM, Smith EM, Wagoner JK. Cancer mortality among nuns: role of the marital status in etiology of neoplastic disease in women. *Journal of the National Cancer Institute* 1969;**42**:455–68.

11 Pereyra AJ. The relationship of sexual activity to cervical cancer. *Obstet Gynecol* 1961;**17**:154–9.

12 Audet-Lapointe P. Detection of cervical cancer in a women's prison. *Can Med Assoc J* 1971;**104**:509–11.

13 Keighley E. Carcinoma of the cervix among prostitutes in a women's prison. *British Journal of Venereal Diseases* 1966;**44**:254–5.

14 Beral V. Cancer of the cervix: a sexually transmitted infection? *Lancet* 1974;i:1037–40.

15 Harris RWC, Brinton LA, Cowdell RH, *et al.* Characteristics of women with dysplasia or carcinoma in situ of the cervix uteri. *Br J Cancer* 1980;**42**:359–67.

16 Kessler II. Venereal factors in human cervical cancer. *Cancer* 1977;**39**:1912–9.

17 Stewart HL, Dunham LJ, Casper J, *et al.* Epidemiology of cancers of the uterine cervix and corpus, breast and ovary in Israel and New York City. *Journal of the National Cancer Institute* 1966;**37**:1–95.

18 Pridan H, Lilienfeld AM. Carcinoma of the cervix in Jewish women in Israel 1960–1967. *Isr J Med Sci* 1971;**7**:1465–70.

19 Handley WS. The prevention of cancer. *Lancet* 1936;i:987–91.

20 Rotkin ID. A comparison review of key epidemiological studies in cervical cancer related to current searches for transmissible agents. *Cancer Res* 1973;**33**:1353–67.

21 Schachter A, Avraham E. Changing trends of cervical neoplasia in Israeli Jews. *Lancet* 1984;ii:1150.

22 Martin CE. Marital and coital factors in cervical cancer. *Am J Public Health* 1967;**57**:803–14.

23 Buckley JD, Harris RWC, Doll R, Vessey MP, Williams PT. Case-control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. *Lancet* 1981;ii:1010–5.

24 Skegg DCG, Corwin PA, Paul C, Doll R. Importance of the male factor in cancer of the cervix. *Lancet* 1982;ii:581–3.

25 Smith PG, Kinlen LJ, White GC, Adelstein AM, Fox AJ. Mortality of wives of men dying with cancer of the penis. *Br J Cancer* 1980;**41**:422–8.

26 Graham S, Priore R, Graham M, Browne R, Burnett W, West D. Genital cancer in wives of penile cancer patients. *Cancer* 1979;**44**:1870–4.

27 Martinez I. Relationship of squamous cell carcinoma of the cervix to squamous cell carcinoma of the penis. *Cancer* 1969;**24**:777–80.

28 Levin ML, Kress LC, Goldstein H. Syphilis and cancer. *NY State J Med* 1942;**42**:1737–45.

29 Rojel J. The interrelation between uterine cancer and syphilis. A pathodemographic study. *Acta Pathol Microbiol Scand (Suppl)* 1953;**97**:13–82.

30 Anderson ER. Possible etiologies of cancer of the cervix other than herpesviruses. *Cancer Res* 1973;**33**:1485–90.

31 Oriel JD, Johnson AL, Barlow D, Thomas BJ, Nayyar K, Reeve P. Infection of the uterine cervix by *Chlamydia trachomatis. J Infect Dis* 1978;**137**:443–51.

32 Swanson J, Eschenbach DA, Alexander ER, Holmes KK. Light and electron microscopic study of *Chlamydia trachomatis* infection of the uterine cervix. *J Infect Dis* 1975;**131**:678–87.

33 McCormack WM, Alpert S, McComb DE, Nichols RL, Semine Z, Zinner SH. Fifteen month follow-up of women infected with *Chlamydia trachomatis. N Engl J Med* 1979;**300**:123–5.

34 Paavonen J, Vesterinen E, Meyer B, *et al.* Genital *Chlamydia trachomatis* infections in patients with cervical atypia. *Obstet Gynecol* 1979;**54**:289–91.

35 Hare MJ, Thin RN. Chamydia infection of the lower genital tract in women. *Br Med Bull* 1983;**39**:138–44.

36 Schachter J, Hill EC, King EB, *et al. Chlamydia trachomatis* and cervical neoplasia. *JAMA* 1982;**248**:2134–8.

37 Briggs RM, Paavonen J. Cervical intraepithelial neoplasia. In: Holmes KK, Mårdh P-A, Sparling PF, Weisner PJ, eds. *Sexually Transmitted Diseases.* New York: McGraw Hill, 1983:589–615.

38 Evans AS. The causes of cancer: viruses. In: Schottenfeld D, Fraumeni JF, eds. *Cancer epidemiology and prevention.* Philadelphia: WB Saunders, 1982:364–90.

39 Weiss RA. Viruses and human cancer. In: Mahy BWJ, Pattison JR, eds. *The microbe. Part 1: Viruses.* Cambridge: Cambridge University Press, 1984:211–40.

40 Pitot HC. *Fundamentals of oncology.* 3rd ed. New York and Basel: Marcel Dekker Inc., 1986;78–80.

41 Nahmias AJ, Sawanabori S. The genital herpes-cervical cancer hypothesis—10 years later. *Prog Exp Tumor Res* 1978;**21**: 117–39.

42 Adam E, Kaufman RH, Melnick JL, Levy AH, Rawls WE. Seroepidemiologic studies of herpesvirus type 2 and carcinoma of the cervix III Houston, Texas. *Am J Epidemiol* 1972;**96**: 427–42.

43 Duff R, Kreider JW, Levy BM, Katz M, Rapp F. Comparative pathology of cells transformed by herpes simplex virus type 1 or type 2. *Journal of the National Cancer Institute* 1974;**53**:1159–64.

44 Aurelian L, Manak MM, McKinley M, Smith CC, Klacsmann KT, Gupta PK. "The herpesvirus hypothesis"—are Koch's postulates satisfied? *Gynecol Oncol* 1981;**12**:556–87.

45 Eglin RP, Sharp F, MacLean AB, Macnab JCM, Clements JB, Wilkie NM. Detection of RNA complementary to herpes simplex virus DNA in human cervical squamous cancer neoplasms. *Cancer Res* 1981;**41**:3597–603.

46 Galloway DA, McDougall JK. The oncogenic potential of herpes simplex viruses: evidence for a "hit and run" mechanism. *Nature* 1983;**302**:21–4.

47 Franceschi S, Doll R, Gallwey J, La Vecchia C, Peto R, Spriggs AI. Genital warts and cervical neoplasia: an epidemiological study. *Br J Cancer* 1983;**48**:621–8.

48 Vonka V, Kanka J, Kremar M, Suchankova A, Zavadova H, Jelinek J. Prospective study on the association between herpes simplex type 2 and cervical neoplasia. In: de Palo G, Rilke F, zur Hausen H, eds. *Herpes and papilloma viruses,* New York: Serono Symposia Publications and Raven Press, 1986:45–53.

49 Nahmias AJ, Naib ZM, Josey WE, Franklin E, Jenkins R. Prospective studies of the association of genital herpes simplex infections and cervical neoplasia. *Cancer Res* 1973;**33**:1491–7.

50 Gissman L. Papillomaviruses and their association with cancer in animals and in man. *Cancer Surveys* 1984;**3**:161–81.

51 McCance DJ. Human papillomaviruses and cancer. *Biochim Biophys Acta* 1986;**823**:195–205.

52 Gissmann L, Schwartz E. Persistence and expression of human papillomavirus DNA in genital cancer. In: Evered D, Clark S, eds. *Papillomaviruses.* Ciba Foundation Symposium 120, Chichester: Wiley:190–207.

53 McCance DJ, Kalache K, Ashdown K, Andrade-Menezes F, Smith P, Doll R. Human papillomavirus types 16 and 18 in carcinoma of the penis from Brazil. *Int J Cancer* 1986;**37**:55–60.

54 Lorincz AT, Lancaster WD, Kurman RJ, Jenson AB, Temple GF. Characterisation of human papillomaviruses in cervical neoplasms and their detection in routine clinical screening. In: Peto R, zur Hausen H, eds. *Viral etiology of cervical cancer.* Banbury Report 21. New York: Cold Spring Harbor Laboratory, 1986:225–37.

55 Durst M, Kleinheinz A, Holtz M, Gissmann L. The physical state of human papillomavirus type 16 DNA in benign and malignant genital tumours. *J Gen Virol* 1985;**66**:1515–22.

56 Walker PG, Singer A, Dyson JL, *et al.* The prevalence of human papillomavirus antigen in patients with cervical intraepithelial neoplasia. *Br J Cancer* 1983;**48**:99–101.

57 Gissmann L, Schneider A. The role of human papillomaviruses in genital cancer. In: de Palo G, Rilke F, zur Hausen H, eds. *Herpes and papilloma viruses*. New York: Serono Symposia Publications and Raven Press, 1986:16–24.

58 Campion MJ, McCance DJ, Cuzixk J, Singer A. Progressive potential of mild cervical atypia: prospective cytological, colposcopic and virological study. *Lancet* 1986;ii:238–40.

59 Cox MF, Meanwell CA, Maitland NJ, Blackledge G, Scully C, Jordan JA. Human papillomavirus type 16-homologous DNA in normal human ectocervix. *Lancet* 1986;ii:157–8.

60 Toon PG, Arrand JR, Wilson LP, Sharp DS. Human papillomavirus infection of the uterine cervix of women without cytological signs of neoplasia. *Br Med J* 1986;**293**:1261–4.

61 Wickenden C, Steele A, Malcolm ADB, Coleman DV. Screening for wart virus infection in normal and abnormal cervices by DNA hybridisation of cervical scrapes. *Lancet* 1985;i:65–7.

62 Baird PJ. Serological evidence for the association of papilloma virus and cervical neoplasia. In: de Palo G, Rilke F, zur Hausen H, eds. *Herpes and papilloma viruses*. New York: Serono Symposia Publications and Raven Press: 1986:83–91.

63 Oriel JD. Genital warts. *Sex Transm Dis* 1977;**4**:153–9.

64 Walker PG, Colley NV, Grubb C, Tejerina A, Oriel JD. Abnormalities of the uterine cervix in women with vulval warts. *British Journal of Venereal Diseases* 1983;**59**:120–3.

65 Syrjanen KJ. Human papillomavirus lesions in association with cervical dysplasias and neoplasias. *Obstet Gynecol* 1983;**62**:617–24.

66 Mitchell H, Drake M, Medley G. Prospective evaluation of risk of cervical cancer after cytological evidence of human papillomavirus infection. *Lancet* 1986;i:573–5.

67 Campion MJ, Singer A, Clarkson PK, McCance DJ. Increased risk of cervical neoplasia in the consorts of men with penile condylomata acuminata. *Lancet* 1985;i:943–5.

68 Yasumoto S, Burckhardt AL, Doniger J, di Paolo JA. Human papillomavirus type 16 DNA-induced malignant transformation of NIH 3T3 cells. *J Virol* 1986;**57**:572–7.

69 Oriel JD. Natural history of genital warts. *British Journal of Venereal Diseases* 1971;**47**:1–13.

70 Meanwell CA, Cox MF, Blackledge G, Maitland NJ. HPV 16 in normal and malignant cervical epithelium: implications for the aetiology and behaviour of cervical neoplasia. *Lancet* 1987;i:703–7.

71 Anonymous. Cervical intraepithelial neoplasia. *Lancet* 1982;ii:365–7.

72 Anonymous. Human papillomaviruses and cervical cancer: a fresh look at the evidence. *Lancet* 1987;i:725–6.

73 Winkelstein W. Smoking and cancer of the uterine cervix: hypothesis. *Am J Epidemiol* 1977;**106**:257–9.

74 Thomas DB. An epidemiological study of carcinoma in situ and squamous dysplasia of the uterine cervix. *Am J Epidemiol* 1973;**10**:19–28.

75 Sasson IM, Haley NJ, Hoffmann D, Wynder EL, Hellberg D, Nilsson S. Cigarette smoking and neoplasia of the uterine cervix: smoke constituents in cervical mucus. *N Engl J Med* 1985;**312**:315–6.

76 Reid BL. Current and future experimental approaches to aetiology. In: Jordan JA, Singer A, eds. *The cervix*. London: WB Saunders, 1976:442–50.

77 French PW, Coppleson M, Reid BL. Effects of sperm protamine on human cervical epithelial cells and BHK 21 cells in vitro. *J Roy Soc Med* 1987;**80**:434–7.

78 Swan SH, Brown WL. Vasectomy and cancer of the cervix. *N Engl J Med* 1979;ii:60–2.

79 Reid BL, French PW, Singer A, Hagan BE, Coppleson M. Sperm basic proteins in cervical carcinogenesis: correlation with socioeconomic class. *Lancet* 1978;ii:60–2.

80 Singer A, Reid BL, Coppleson M. A hypothesis: the role of a high-risk male in the etiology of cervical carcinoma. *Am J Obstet Gynecol* 1976;**126**:110–5.

81 Schneider V, Kay S, Lee HM. Immunosuppression as a high-risk factor in the development of condyloma acuminatum and squamous neoplasia of the cervix. *Acta Cytol* 1983;**27**:220–4.

82 Detels R, Fahey JL, Schwartz K, Greene RS, Visscher BR, Gottlieb MS. Relation between sexual practices and T-cell subsets in homosexually active men. *Lancet* 1983;i:609–11.

83 Frazer IH, Medley G, Crapper RM, Brown TC, Mackay IR. Association between anorectal dysplasia, human papillomavirus and human immunodeficiency virus infection in homosexual men. *Lancet* 1986;ii:657–60.

84 Singer A, Walker P, Tay SK, Dyson J. Impact of introduction of colposcopy to a district general hospital. *Br Med J* 1984;**289**:1049–51.

85 Laara E, Day NE, Hakama M. Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programmes. *Lancet* 1987;i:1247–9.

86 Office of Population Censuses and Surveys. Mortality statistics, cause, 1975. Series DH2 No 1. London: HMSO,1975:1–14.

87 Office of Population Censuses and Surveys. Mortality statistics, cause, 1982. Series DH2 No 9. London: HMSO, 1983:1–10.

88 Richart RM, Barron BA. Screening strategies for cervical cancer and cervical intraepithelial neoplasia. *Cancer* 1981;**47**:1176–81.

89 Walker EM, Dodgson J, Duncan ID. Does mild atypia on a cervical smear warrant further investigation? *Lancet* 1986;ii:672–3.

90 Campion MJ, Singer A, Mitchell HS. Complacency in diagnosis of cervical cancer. *Br Med J* 1987;**294**:1337–9.

91 Maw RD, Hanley O. Cervical cytology figures for 1970–81. *British Journal of Venereal Diseases* 1983;**59**:408–9.

92 Briggs RM, Holmes KK, Kiviat N, Barker E, Eschenberg DA, de Jong R. High prevalence of cervical dysplasia in STD clinic patients warrants routine cytologic screening. *Am J Public Health* 1980;**70**:1212–4.

93 Lyttle H, Platts WM, MacLean AB. Pilot study of cervical cytology screening in a sexually transmitted diseases clinic. *Genitourin Med* 1985;**61**:330–4.

94 British Co-operative Clinical Group. Cervical cytology screening in sexually transmitted diseases clinics in the United Kingdom. *Genitourin Med* 1987;**63**:40–3.

95 Anonymous. Cancer of the cervix: death by incompetence. [Editorial]. *Lancet* 1985;ii:363–4.

96 Kaufman R, Koss LG, Kurman RJ, *et al.* Statement of caution in the interpretation of papillomavirus-associated lesions of the epithelium of the uterine cervix. *Am J Obstet Gynecol* 1983;**146**:125.